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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,795	10/23/2000	Jeffrey D. Rothstein	JHU1650-2	3376

7590 11/26/2003

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	12

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,795	ROTHSTEIN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82 and 84-91* is/are pending in the application.

4a) Of the above claim(s) *1-10,12,14-17,23-82 and 84-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,18-22 and 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 3 July 2003 has been entered. Claim 83 has been cancelled. Claims 11 and 13 have been amended. Claims 89-91 have been added. Claims 1-10, 12, 14-17, 23-82 and 84-88 were previously withdrawn by the examiner. Claims 11, 13, 18-22 and 89-91 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

Informalities

URL's

The objection to the disclosure for containing browser-executable code, as set forth at p. 2-3 of the previous Office Action (1 April 2003), is *withdrawn* in view of the amendment which deleted URL's from the Specification (3 July 2003).

Claim Objections-

The objection to Claims 11 and 83 for depending from non-elected claims is *withdrawn*. Applicants cancelled Claim 83 in the amendment dated 3 July 2003, and removed language from Claim 11 which had previously made it dependent on non-elected Claim 1.

Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.

The rejection of Claim 13 under 35 U.S.C. 112, second paragraph, for reciting language that encompasses a degenerate sequence of a complementary nucleic acid, as set forth at p. 7-8 of the previous Office Action (1 April 2003), is *withdrawn.* The amendment submitted by the Applicant (3 July 2003) deleted the phrase "degenerate variants" from Claim 13, part (e).

Maintained Rejections/Objections

35 USC § 112, first paragraph – Scope of Enablement

Claims 11, 13, 18-22 and 89-91 are rejected under 35 U.S.C. 112, first paragraph because the instant disclosure, while being enabling for the polynucleotide of SEQ ID NO: 3 and the polynucleotides encoding SEQ ID NO: 4, as well as full-length complements, does not reasonably provide enablement for *all* polynucleotides encoding all variants of *GTRAP4-48,* as set forth in Claims 11, 13, 18-22 and 89-91. The reasons for this rejection were set forth at pages 3-7 of the previous office action (1 April 2003). Newly-submitted and amended claims, although referring to SEQ ID NO: 3 or 4, still encompass degenerate and variant polynucleotides. The specification does not provide enough guidance to make all nucleotide variants encompassed by the claims.

Claims 11, 13, 18-22 and 89-91 are directed primarily to polynucleotides encoding *GTRAP4-48*, a cytoskeletal peptide functionally-associated with the glutamate transporter

EAAT4. Dependent claims recite DNA and RNA encoding variants of SEQ ID NO: 4, as well as fragments, vectors, host cells and recombinant methods of producing the *GTRAP4-48* peptide. The specification discloses the polynucleotide of SEQ ID NO: 3, as well as methods for recombinantly expressing the *GTRAP4-48* polypeptide of SEQ ID NO: 4. However, the breadth of claims 11, 13, 18-22 and 89-91 is too large since the applicants are only enabled for the polynucleotide(s) encoding the *GTRAP4-48* polypeptide of SEQ ID NO: 4, but are claiming polynucleotides that are complements to degenerate sequences encoding SEQ ID NO: 4, and polynucleotides where "T *can be* U". In amended Claim 11, for example, the claimed polynucleotide is associated "-*having* an amino acid sequence-" with SEQ ID NO: 4, but is claimed as a polynucleotide that is complementary to a degenerate sequence encoding SEQ ID NO: 4. This combined with "open" language ("characterized as" and "*having* an amino acid sequence") and moderately-stringent hybridization conditions (page 20, Specification), means there are several steps of nucleotide processing, encompassed by the claim, where deviation from SEQ ID NO: 3 can occur. Likewise, Claim 13 encompasses several layers of degeneracy; in Claim 13(a), the polynucleotide encodes a polypeptide "having" the amino acid sequence of SEQ ID NO: 4, as well as claims RNA using open language: "wherein T *can be* U," leading to a very large number of possible variants. The claims embrace an essentially infinite number of polynucleotides encoding an infinite number of *GTRAP* polypeptides.

Applicants point to the combination of structural and functional elements recited in the independent claims (page 9, 3 July 2003) as evidence that the claims do not encompass an infinite number of polynucleotides. They claim that "a skilled artisan can readily determine whether a polynucleotide falls within the claims by performing routine hybridization

experiments under the defined conditions and routine functional experiments using, for example, the methods taught in the specification" (page 9, 3 July 2003).

Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons: As discussed in the previous Office Action (page 6, 1 April 2003), while it is true that the specification contains art-recognized methods for producing and screening for a polynucleotide that "falls within the claims" (page 9-10, 3 July 2003), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to use the current invention as a starting point for further experimentation. Applicant has provided little guidance beyond the presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the GTRAP protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions, while still producing a protein that is the equivalent of SEQ ID NO: 4. Applicants go on to discuss the presence of protein domains within GTRAP4-48, stating that "SEQ ID NO: 4 includes a PDZ domain, a regulatory G-protein domain, a pleckstrin homology region, and a proline-rich sequence" (page 10, 3 July 2003). They cite two papers, presumably as evidence that the GTRAP4-48 domains discussed above help define the GTRAP proteins in predictable ways (Katan and Allen, 1999, FEBS Letters, 452: 36-40; Levine, H 3rd, 1999, Mol. Neurobiol., 19(2): 111-149). However, neither the Katan paper nor the LeVine paper mentions the domains discussed by the Applicant. They do discuss the functional significance of other protein domains, such as the *C2* domain of some phospholipases and synaptotagmins (page 37, Katan and Allen, 1999). Both papers point to numerous types of proteins which have each domain. For example the *C2* domain is found in

both enzymes and cytoskeletal proteins. More importantly when discussing the instant Invention: the domains discussed in the submitted papers function differently in different proteins and contribute differently to the overall function of the proteins in which they are found. This demonstrates that the presence of a recognized functional domain within a protein is not a clear indication of the overall function of a protein within a cell or organism. Applicant's statements amount to an affirmation that the claimed subject matter functions as it was intended to function. The references provided are not relevant to the issue of the breadth of enablement of the claimed subject matter and provide no objective evidence thereto (see MPEP § 716).

Applicants go on to discuss the usefulness of the claimed polynucleotides in terms of probes for detecting the polynucleotides that encode all or a portion of SEQ ID NO: 4 (page 11, 3 July 2003). However, the usefulness of probes for a polynucleotide is generally directly related to the usefulness of the polynucleotide for which the complements are made. In addition, as far as a probe's usefulness in detecting the nucleotide encoding SEQ ID NO: 4, it is most useful to have a probe with a well-defined sequence, at least as well-defined as the nucleotide being detected. The specification does not teach all possible fragments of SEQ ID NO: 3 that hybridize to a polynucleotide encoding the polypeptide consisting of the amino acid sequence of SEQ ID NO: 4. Additionally, since claims of the instant application recite polynucleotide fragments hybridizing to a polynucleotide encoding the polypeptide of SEQ ID NO: 4, the claims encompass codon degeneracy. The skilled artisan is not able to predict what the polynucleotide-encoding sequence is from an amino acid sequence and therefore use of a degenerate sequence as a probe does not come with a reasonable expectation of success.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to: generate the infinite number of derivatives recited in the claims and screen all variants for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite adequate structural or functional limitations--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion: Claims 11, 13, 18-22 and 89-91 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. (Note: after 21 January 2004, the Examiner's phone number will be (571) 272-0895). The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW
11/14/03

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER